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Bronchiolitis obliterans organizing pneumonia in cancer: a case series

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Abstract Bronchiolitis obliterans with organizing pneumonia (BOOP) is an infrequently encountered clinical condition that can mimic a number of other pathologic lung processes. The presentation of this treatable condition in cancer patients has not been described in any large series. We conducted a retrospective study of patients with BOOP at Memorial Sloan–Kettering Cancer Center, New York, NY, U.S.A. from January 1992 to December 1999. The type and treatment of primary cancer, clinical and radiographic features of initial BOOP presentation, and outcome following therapy were recorded. Forty-three patients with an underlying diagnosis of cancer were found on lung biopsy to have BOOP as an isolated entity. BOOP was encountered in patients with a variety of clinical presentations, and many types of malignancies. The symptom patterns were non-specific, as were the physiological abnormalities. The only clear relationship between the underlying malignancy and the diagnosis of BOOP at presentation was in the chest radiographic findings. Patients with solid organ tumors were more likely to have nodular or mass like radiographic abnormalities (81%) than to have diffuse infiltrates (19%). We observed the opposite pattern in patients with hematologic malignancies (22% *vs*.67%). The vast majority of patients recovered from this condition. In conclusion, For cancer patients, BOOP represents a treatable cause of lung disease with protean manifestations. BOOP can mimic pulmonary malignancy and pulmonary infection. In cancer patients, the evaluation of new pulmonary symptoms accompanied by radiographic changes should include a consideration of this diagnosis.

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Keywords lung; bronchiolitis obliterans organizing pneumonia; neoplasm.

INTRODUCTION

Patients with active or previously treated cancer who develop new pulmonary symptoms or abnormal chest radiographs are frequently encountered. Typically, the first concern is either progression of cancer or an infectious process. In the past several years, bronchiolitis obliterans with organizing pneumonia (BOOP) has been found to be the underlying lung process in some of these patients. Lange, a German pathologist, first described the pathological findings of BOOP in two autopsies in 1901 (1). In 1985, Epler *et al*. published the first comprehensive clinical case series of these patients, identifying BOOP as a distinct clinical entity with features of both pneumonia and airways abnormalities (2). BOOP is characterized by the formation of granulation tissue plugs (*i.e*. Masson bodies) within the lumen of small airways, alveolar ducts and alveoli. These consist of rounded balls of myxomatous connective tissue that form intra-luminal polyps within bronchioles and air spaces. Inflammatory cells including neutrophils, lymphocytes and plasma cells are sometimes seen at the center of the intra-luminal myxoid polyps. Other features include intra-alveolar foamy macrophages, fibrinous exudates and an interstitial mononuclear cell infiltrate of variable density (3) (Fig. 1).

The underlying cause of BOOP remains unknown, although its association with variety of conditions such as bacterial (4), viral (5), parasitic (6) and fungal (7) infections, collagen vascular disease (8–11), drug toxicity (12) and inhalation of toxic fumes (13) have all been described. When BOOP has been reported in cancer patients, it has mostly been in the setting of allogeneic bone marrow transplanatation (14) or in breast cancer patients receiving radiation therapy (15). A systematic association with other types of cancer has not been reported. In this study, we report the clinical manifestations, treatment, and outcomes of a consecutive series of cancer patients with pathologically proven BOOP seen at our institution.

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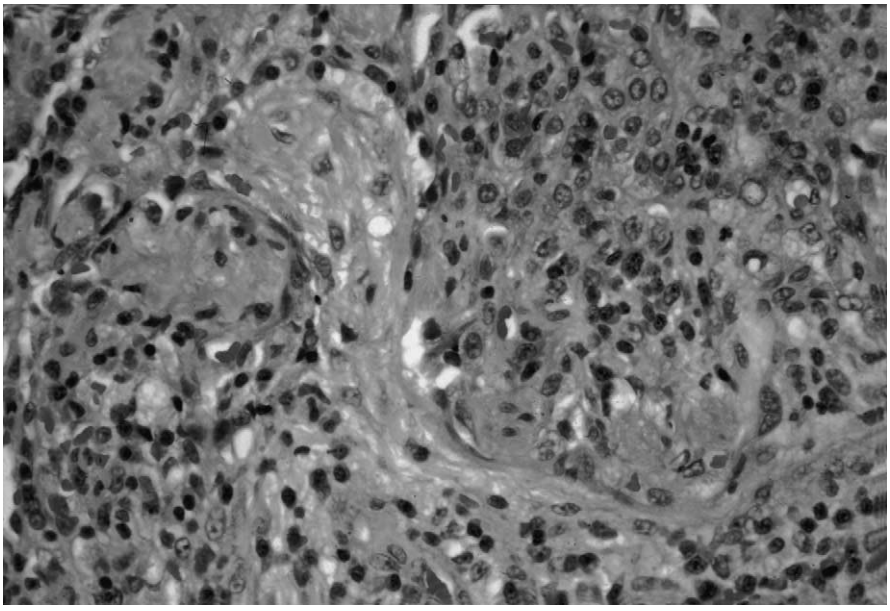

Fig. 1. Pathology photomicrograph (H&E stain × 20) of an open lung biopsy from a patient with leukemia and BOOP, showing a fibroblastic plug filling the air spaces and includes foamy macrophages and inflammatory cells with interstitial pneumonia and air space fibrosis.

MATERIALS AND METHODS

Patient data

Patients with an antecedent or concomitant diagnosis of cancer and pathological evidence of BOOP are the subjects of this study. We report the clinical features, radiographical abnormalities, treatment and outcome of these patients, who received their care at Memorial Sloan–Kettering Cancer Center (MSKCC) during the years 1992–1999. These patients had undergone lung biopsy for the evaluation of undiagnosed pulmonary nodules, masses or infiltrates. Although BOOP has frequently been observed in the immediate vicinity of other lung processes, the patients included in this series all had the pathologic diagnosis of BOOP in an isolated region of the lung, exclusive of malignancy, granuloma or infection. The patients were identified through a computerized search of the MSKCC pathology database, supplemented by a search of pathological slides submitted from other institutions. Those patients who did not receive their care at the MSKCC were excluded from the study.

Patient information was abstracted from the paper charts and computerized medical record system of MSKCC. Age, sex, ethnicity, smoking history, cancer information such as date and method of the diagnosis, stage, chemotherapeutic regimen, radiation treatment, bone marrow transplantation, conditioning regimens, infection and graft versus host disease (GVHD) prophylactic protocols, and complications of therapy were documented.

Symptoms and signs present at the time of diagnosis of BOOP were abstracted from the medical record. Other information, such as pulmonary function tests, radiographical findings and descriptions of histopathology were adapted from the official report. Treatments received and patient outcomes, including radiographical changes and survival time after BOOP diagnosis were obtained from the medical charts and from conversations with patients and providers. Cause of death was determined through the treating physician's reports.

Definitions of variables

Pulmonary function

Pulmonary function tests included spirometry (before and after bronchodilators, if indicated), lung volumes and single-breath carbon monoxide diffusion capacity (DL_{CO}). Spirometry was performed on a Warren E. Collins modular unit using the standard spirometric techniques. Volumes were determined by the closed-circuit helium dilusion method. The DL_{CO} was determined by the method of Ogilvie *et al*. and Cotes *et al*. Exercise testing was done measuring pulse oximetry before, during and after 30 sec of activity using the Masters two-step staircase. Pulmonary function tests were performed and interpreted based on the American Thoracic Society (ATS) criteria delineated in the ATS official statement on standardization of spirometry (16,17). Patients characterized as having oxygen desaturation were those who dropped their oxygen saturation four or more

percentage points from resting oxygen saturation during 1·5 min on a Masters two-step staircase (18).

Radiographical features

The radiographical features were classified based on the dimensions, distribution, and characteristics of the abnormality. A *nodule* was defined as a well-circumscribed lesion with the largest dimension measuring 3 cm or less on plain chest radiography or CT scan. A *mass* was defined as a well-circumscribed lesion greater than 3 cm in its greatest dimension. *Infiltrative* patterns were defined as vaguely circumscribed abnormalities of interstitial or alveolar origin or consolidation with air-bronchogram that involved one or more lobes. Ground glass attenuation based on the CT findings, when available, were incorporated.

Pulmonary toxic agents

A history of radiation to the chest wall and a history of receiving chemotherapeutics with known pulmonary toxicity were identified from the patients' charts and correspondence with other treating facilities. Agents administered which were considered to have pulmonary toxicity included: bleomycin, gemcitabine, mitomycin-C, methotrexate, taxol, ATRA, ara-C, vinca alkaloids, nitrosoureas and alkylating agents, particularly *cyclophosphamide*.

Outcome

Data regarding patient outcome such as symptomatic and radiographic changes in response to therapy, mortality data related to respiratory decompensation within 30 days of BOOP diagnosis and other causes of deaths unrelated to BOOP were documented from the physician reports.

Statistical analysis

Most of the results presented in this paper are descriptive in nature and are presented as summary statistics. The exceptions include: association between underlying malignancy and chest radiographical findings was evaluated using Fisher's exact test (19) and changes in pulmonary function tests over time were assessed using the Student's *t*-test (20). All *P*-values quoted are two-sided.

RESULTS

Study patients

Lung tissue specimens from 8519 were accessioned by the Pathology Department of MSKCC between February 1992 and August 1999. Sixty-eight had pathological evidence of BOOP. Twenty-five of the patients were excluded from the study because BOOP was located in a region of another pathological process or processes. Of the remaining 43 patients with isolated BOOP, pathological specimens were obtained by surgical resection or open lung biopsy through formal thoracotomy in 29 (68%) patients, video-assisted thoracoscopic surgery (VATS) in 10 (23%) patients and transbronchial biopsy through fiber-optic bronchoscopy in four (9%) patients.

The mean age of the patients was 57·4 (20–89) years. White males with history of 20 or more pack-years of smoking formed the major group. The study patients had a wide variety of malignancies. Twenty-seven (63%) had solid organ tumors and 16 (37%) had hematological malignancies with some form of leukemia or lymphoma; nine (21%) and seven (16%) respectively (Table 1).

Table 1. Characteristics of 43 patients with pathologically proven bronchiolitis obliterans organizing pneumonia (BOOP) between 1992 and 1999 at the Memorial Sloan–Kettering Cancer Center

Age in years (mean, range)	57·4 (20–89)
Sex	
Male	29 (67%)
Female	14 (33%)
Race	
Caucasian	36 (84%)
Hispanic	3 (7%)
Others	4 (9%)
Smoking history	
Non-smokers	14 (32%)
20 pack-years or more	21 (49%)
20 pack-years or less	8 (19%)
Malignancy	
Solid organ tumors 27 (63%)	
Non-small cell lung cancer (NSCLCA)	8 (19%)
Small cell lung cancer	2 (5%)
Sarcoma	4 (10%)
Germ cell	3 (7%)
Gastrointestinal	3 (7%)
Melanoma	2 (5%)
Prostate	1 (2%)
Thymoma	1 (2%)
Breast	1 (2%)
Multiple malignancies	
colon adenocarcinoma/transitional cell carcinoma of the urinary bladder	1 (2%)
NSCLCA/prostate	1 (2%)
Hematologic malignancies 16 (37%)	
Lymphoma	7 (16%)
Leukemia	9 (21%)
Allogeneic bone marrow transplanation	9 (21%)
Leukemia	8 (19%)
Lymphoma	1 (2%)

Prior treatment

All patients had undergone treatment for their malignancy. Thirty-one (72%) patients received more than one mode of treatment. Eight had chemotherapy and surgery, six had chemotherapy and radiation, three had radiation followed by surgery, five had chemotherapy, radiation and surgery and nine underwent allogeneic bone marrow transplantation after preparation with chemotherapy and total body irradiation. Of those patients who received single modality treatment, seven had surgery and five had chemotherapy.

Nine of the patients in our series had a history of receiving radiation therapy. Two had extra-thoracic radiation only and these individuals developed BOOP 2–3 years after their treatment. Of the seven who had radiation therapy to the chest, all developed BOOP within 120 days (BOOP was found ipsilateral to the radiation port in five of these patients).

Thirty-one (74%) patients had chemotherapy. Vincristine, cisplatin, cyclophosphamide and taxol were the most frequent agents used as a single or combination therapy in descending order. In total 15 (35%) patients received agents with known pulmonary toxicity and only three patients received bleomycin, an agent that has been reported to have an association with BOOP (21). Other chemotherapeutic agents such as ifosfamide, velban, methotrexate and mitomycin were used with less frequency in this population.

Clinical presentation of BOOP

Clinical symptoms (Tables 2 and 3)

Symptoms were experienced by 33 (77%) of patients, including cough (60%), sputum production (39%) and dyspnea (38%). In only half of these patients (17 of 33) was fever a prominent component. Chest pain (7%) and hemoptysis (5%) were relatively rare. Generalized fatigue was the predominant non-pulmonary symptom. Symptoms were more common in patients with infiltrative radiographic finding (14 of 15) compared with those who had nodules or masses (19 of 28).

Table 2. Common pulmonary and non-pulmonary symnptom(s) reported by the 43 patients with bronchiolitis obliterans organizing pneumonia and malignancy

Symptoms	
Cough	26 (60%)
Sputum	17 (39%)
Dyspnea	16 (37%)
Fever	13 (30%)
Chest pain	3 (7%)
Cough, dyspnea, sputum and fever	14 (33%)
Hemoptysis	2 (5%)
Generalized fatigue	4 (9%)
None	10 (23%)

Chest radiographical findings

The study subjects had a variety of chest radiographical abnormalities. We noted an association between the underlying malignancy and radiographic finding that did not reach statistical significance ($P = 0 \cdot 15$). The majority of patients with solid organ tumors had nodules or masses as the manifestation of BOOP. In contrast, BOOP in patients with hematological malignancies were more likely to appear as an infiltrative pattern on chest radiographs (Figs 2 and 3).

Pulmonary function data

Twenty-five (58%) patients had pulmonary function testing (PET) prior to the diagnosis of BOOP. Thirteen (30%) patients demonstrated obstructive or mixed ventilatory

Table 3. Relationship of the radiographical findings to symptoms, treatment and outcome in 43 patients with BOOP and malignancy

Symptoms, Treatment and Outcome	*n* (% total)	Chest radiographical features	
		Nodular/mass-like, *n*=28 (65%)	Infiltrate, *n*=15 (35%)
Symptoms			
Symptomatic	33/43 (77%)	19/28 (68%)	14/15 (93%)
Asymptomatic	10/43 (23%)	9/28 (32%)	1/15 (7%)
BOOP treatment			
No medical treatment	21/43 (49%)	19/28 (68%)	2/15 (13%)
Steroids	20/43 (46%)	8/28 (28%)	12/15 (80%)
Macrolides	2/43 (5%)	1/28 (4%)	1/15 (7%)
Outcome			
Treated and alive by the end of study	29/43 (67%)	24/28 (86%)	5/15 (33%)
BOOP unrelated death	11/43 (26%)	4/28 (14%)	7/15 (47%)
Respiratory death (within 30 days of BOOP diagnosis)	3/43 (7%)	0/28 (0%)	3/15 (20%)

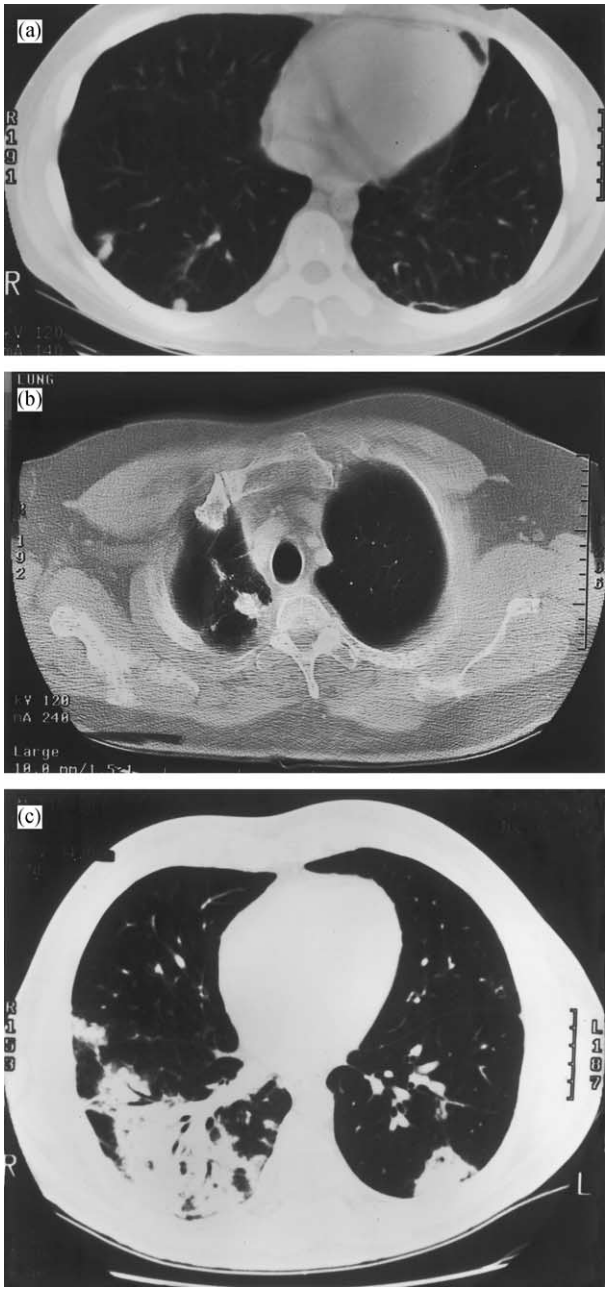

Fig. 2. CT scans of the chest in three patients with malignancy and BOOP on open lung biopsy or resection. (a) A patient with testicular cancer and pulmonary nodules, (b) mass in the right upper lung field in a patient after lobectomy for NSCLCA and (c) nodular infiltrate in a patient with acute myelogenous leukemia during chemotherapy.

defects; of these, nine (70%) had greater than 20 pack-years of smoking. In contrast, only two patients had isolated restrictive defects; the PFT abnormality most commonly associated with BOOP (2). For the 17 (39%) patients with available post-treatment PFT, we observed small but consistent declines in forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1) and

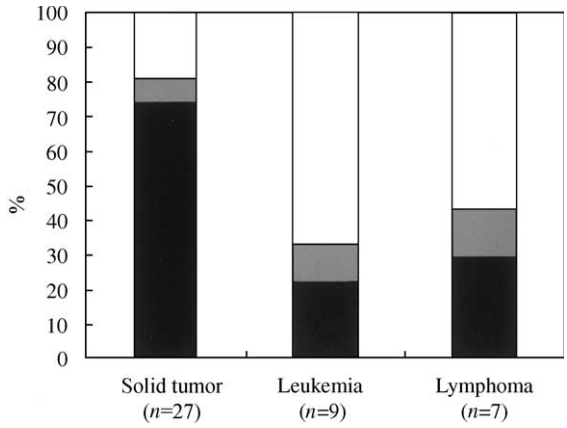

Fig. 3. A bar graph illustrating the relationship of radiographical patterns and the type of underlying malignancy in 43 patients with cancer and BOOP. Nodules (■), mass (▩) and infiltrate (□).

DL_{CO} that were not statistically significant (data not shown). Exercise oxygen desaturation was noted in five (12%) patients. One patient in this group had hematological malignancy with diffuse infiltrative chest radiographic findings. The rest were in the solid organ tumor group with smoking history and nodular chest radiographic abnormalities.

Antecedent infections

A total of four patients had antecedent evidence of pulmonary cytomegalovirus (CMV) disease detected from bronchoscopy specimens. All of these patients had received allogenic bone marrow transplantation before 1994. We have not seen any pulmonary CMV disease in this series after 1994. Other infections encountered in association with BOOP at diagnosis were *Cryptococcosis neoformans, Pneumocystis carinii, Hemophillus influenza and Mycofacterium, tuberculosis*, each found in one patient.

Patient treatment and outcome

Twenty-one (49%) patients received no specific medical therapy. Of these, sixteen (76%) patients had solid organ tumor and five (24%) had hematological malignancies. In this group 10 (23%) patients were asymptomatic and the remainder had resolution of their symptoms after surgical resection of lung lesion(s). Of the symptomatic patients, 20 (46%) patients were treated with corticosteroids for a minimum period of 4 months (typical dose 40–60 mg of prednisone per day) and two (5%) received macrolides due to steroid intolerance. Seventy-five per cent of medically treated patients had hematological malignancy whereas amongst patients with solid organ tumor 29% required medical therapy for their

BOOP. Three (7%) patients died of a respiratory cause within 1 month of BOOP diagnosis—all of these patients belong to the hematological malignancy group, had more severe respiratory symptoms, had infiltrative pattern on chest radiographs and required steroid therapy. Eleven (26%) patients died due to causes unrelated to BOOP while 29 (67%) became symptom-free and had complete normalization of their chest radiographs. Of these patients, 14 (47%) had never received treatment for BOOP, while the remainder had received either corticosteroids or macrolide therapy. One patient demonstrated radiographical relapse of BOOP that was attributed to steroid intolerance. This patient had subsequently complete symptomatic and radiographical resolution of her disease after low dose macrolide therapy. Pathologically proven relapse has not been documented in this group to date.

DISCUSSION

Patients with pulmonary abnormalities who have either antecedent or ongoing cancer are frequently encountered in our medical center. This study focuses on the clinical presentation and outcome of those patients with radiographical abnormalities who ultimately were found to have pathologically proven BOOP. We identified 43 cases of isolated BOOP from a total of 8519 lung pathological slides that were accessioned between 1992 and 1999 at the Memorial Sloan–Kettering Cancer Center.

Cordier et al. divided patients with BOOP in to two groups based on radiographic patterns and used this classification to predict outcome in each group. Patients with localized disease were rarely symptomatic and had overall a good prognosis, whereas patients with diffuse disease were more often symptomatic, required treatment with corticosteroids and had variable outcomes (12). Through this study we have also observed a similar radiographical distinction. Furthermore, we found that the type of the underlying malignancy frequently could be correlated to the clinical course, radiographical findings and patient outcome. We classified our patients with malignancy and BOOP into two major categories, those with solid organ tumors and those with hematological malignancies. The majority of patients with solid organ tumors had nodular or mass-like radiographical findings, were either asymptomatic or had minimal respiratory symptoms, did not require treatment, and had better outcomes. The patients with hematological malignancies more frequently had patchy or diffuse infiltrative chest radiographical findings, had pronounced respiratory symptoms (particularly those with leukemia who underwent allogenic bone marrow transplantation), required antiinflammatory therapy for BOOP and had complicated course. All three BOOP-related mortalities occurred in this group.

The close correlation of the clinical course and outcome with the underlying malignancy may be due to several factors. In patients with hematological malignancies, the pulmonary disease is usually more advanced at presentation as evidenced by the diffuse rather than localized infiltrates. Because of the diffuse nature of BOOP in this group, and often the low pulmonary reserve secondary to extensive prior chemotherapy and/or chest irradiation, surgical resection is not an option.

There have been many reports of BOOP in association with infectious diseases. Several patients in our study had previous cytomegalovirus infection and one had *Hemophillus influenza* infection. We were, however, unable to identify a statistically significant relationship between any specific pathogen and the development of BOOP. Furthermore, we were unable to determine any statistically significant correlation between the occurrence of BOOP in malignancy and any particular chemotherapeutic agent or thoracic irradiation. In a large number of patients pulmonary function testing indicated a pattern of obstructive airways disease that was likely due to the smoking. Presence of infiltrates or consolidation on the chest roentgenograms did not correlate with a restrictive ventilatory defect on pulmonary function studies.

Approximately half of our patients were given specific treatment for BOOP and the vast majority of these received corticosteroid therapy. Two patients were managed successfully with low dose macrolides alone secondary to steroid intolerance. The idiopathic form of BOOP has excellent prognosis with a mortality of less than 5% (22). The higher BOOP related mortality in our group (7%), is probably multifactorial. Prior lung injury secondary to chemotherapy, chest irradiation and overall altered immune status due to the malignant process or long term steroid therapy, particularly in patients with hematological malignancies, in part may have caused a poorer outcome. Because macrolides could be potentially offered as a steroid-sparing agent, secondary to their inherent anti-inflammatory property, studies should be undertaken to evaluate their efficacy in treatment of BOOP.

There are some limitations to this study. The true incidence of BOOP in cancer patients cannot be determined. We only reviewed the patients who were diagnosed from a lung biopsy. Presumably, we have provided care to a number of patients with BOOP based on clinical and radiographical suspicion without a pathological diagnosis. In addition, the outcome data we present is limited in some cases by the level of detail we were able to obtain from telephone interviews of patients and outside providers in some cases.

When confronted with a cancer patient with a new pulmonary process, the typical concerns are either infection or progression of malignancy. In our patients, BOOP presented in a variety of ways that might be consistent

with one of these two diagnoses. As the treatment of BOOP is different from these other conditions, and the anticipated outcome given proper treatment is excellent, clinicians should consider this diagnosis when evaluating a cancer patient with a new pulmonary process. The association we have noted between radiographical appearance and underlying malignancy should also be helpful in this clinical situation.

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